

We claim:

1. A method for producing biocompetent fibrinogen comprising: 30

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen A $\alpha$  chain,

the DNA segment comprising genomic DNA encoding the A $\alpha$  chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen B $\beta$  chain,

the DNA segment comprising genomic DNA encoding the B $\beta$  chain; and

a third DNA segment encoding a secretion 35  
signal operably linked to a heterologous fibrinogen  $\gamma$  chain.

the DNA segment comprising genomic DNA encoding the  $\gamma$  chain,

wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host 40 female mammal;

introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said egg into an oviduct or uterus of a female of 45 said mammalian species to obtain offspring carrying said DNA segments;

breeding said offspring to produce female progeny that express said first, second and third DNA segments and produce milk containing biocompetent fibrinogen 50 encoded by said segments;

collecting milk from said female progeny; and  
and recovering the biocompetent fibrinogen from the milk.

2. A method according to claim 1 wherein said species 55 into which said DNA segments are introduced is selected from the group consisting of sheep, pigs, goats, and cattle.

3. A method according to claim 1 wherein each of said first, second and third DNA segments comprises an intron.

4. A method according to claim 1 wherein the molar ratio 60 of said first, second and third DNA segments is within the range of 0.5-1:0.5-1:0.5-1.

5. A method according to claim 1 wherein each of said first, second and third DNA segments is operably linked to a transcription promoter selected from the group consisting 65 of casein,  $\beta$ -lactoglobulin,  $\alpha$ -lactalbumin and whey acidic protein gene promoters.

6. A method according to claim 1 wherein said first, second and third DNA segments are expressed under the control of a  $\beta$ -lactoglobulin promoter.

7. A method according to claim 1 wherein said introducing step comprises injecting said first, second and third DNA segments into a pronucleus of said fertilized egg.

8. A method according to claim 1 wherein said fibrinogen is human fibrinogen.

9. A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 470 to nucleotide 8100.

10. A method according to claim 1 wherein said second DNA segment comprises a sequence of nucleotides as shown in SEQ ID NO: 3 from nucleotide 512 to nucleotide 8100.

11. A method according to claim 1 wherein said species into which said DNA segments is introduced is sheep.

12. A method of producing biocompetent fibrinogen comprising:

incorporating a first DNA segment encoding a secretion signal operably linked to an A $\alpha$  chain of fibrinogen into a  $\beta$ -lactoglobulin gene to produce a first gene fusion comprising a  $\beta$ -lactoglobulin promoter operably linked to the first DNA segment

, the DNA segment comprising genomic DNA encoding the A $\alpha$  chain;

incorporating a second DNA segment encoding a secretion signal operably linked to a B $\beta$  chain of fibrinogen into a  $\beta$ -lactoglobulin gene to produce a second gene fusion comprising a  $\beta$ -lactoglobulin promoter operably linked to the second DNA segment

, the DNA segment comprising genomic DNA encoding the B $\beta$  chain;

60 incorporating a third DNA segment encoding a secretion  
 signal operably linked to a  $\gamma$  chain of fibrinogen into a  
 $\beta$ -lactoglobulin gene to produce a third gene fusion  
 comprising a  $\beta$ -lactoglobulin promoter operably linked  
 to the third DNA segment

, the DNA segment comprising  
genomic DNA encoding the  $\gamma$   
chain,

wherein each of said first,  
 second and third segments are of the same species;  
 65 introducing said first, second and third gene fusions into  
 the germ line of a non-human mammal so that said  
 DNA segments are expressed in a mammary gland of

obtaining milk from said mammal or its female progeny;  
and

13. A method according to claim 12 wherein said mammal is a sheep, pig, goat or cow.

15. A method according to claim 12 wherein the molar ratio of said first, second and third gene fusions introduced is within the range of 0.5-1:0.5-1:0.5-1.

17. A method according to claim 12 wherein said mammal is a sheep.

providing a transgenic female non-human mammal carrying in its germline heterologous

### DNA segments

collecting milk from said mammal; and

19. A method according to claim 18 wherein said mammal is a sheep, pig, goat or cow.

21. A transgenic non-human female mammal that produces recoverable amounts of biocompetent human fibrinogen in its milk, wherein said mammal comprises:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen A $\alpha$  chain,

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen B $\beta$  chain.

and

a third DNA segment encoding a secretion signal operably  
linked to a heterologous fibrinogen  $\gamma$  chain.

the DNA segment comprising  
heterologous genomic DNA  
encoding the y chain;

and  
further wherein each chain is derived from the same species  
and is operably linked to additional DNA segments required  
for its expression in the mammary gland of a host female  
mammal.

22. A mammal according to claim 21 wherein said mammal is a sheep.

23. A process for producing a transgenic offspring of a mammal comprising:

- 5 providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen A $\alpha$  chain,

the DNA segment comprising genomic DNA encoding the A $\alpha$  chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen B $\beta$  chain,

the DNA segment comprising genomic DNA encoding the B $\beta$  chain;

- 10 and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen  $\gamma$  chain,

the DNA segment comprising genomic DNA encoding the  $\gamma$  chain,

wherein each chain is derived from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

- 15 introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains; inserting said fertilized egg into an oviduct or uterus of a female of said mammalian species; and  
20 allowing said fertilized egg to develop thereby producing transgenic offspring carrying said first, second and third DNA segments, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen.

- 25 24. A process according to claim 23 wherein said offspring is female.

25. A process according to claim 23 wherein said offspring is male.

- 30 26. A non-human mammal produced according to the process of claim 23.

27. A non-human mammal according to claim 26 wherein said mammal is female.

- 35 28. A non-human female mammal according to claim 27 that produces milk containing biocompetent fibrinogen encoded by said DNA segments.

29. A non-human mammal according to claim 26 wherein said mammal is male.

30. A non-human mammal carrying in its germline

heterologous genomic

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33. A mammal according to claim 30, wherein said mammal is a sheep.



34. A set of DNA sequences comprising:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen A $\alpha$  chain, the DNA segment comprising genomic DNA encoding the A $\alpha$  chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen B $\beta$  chain, the DNA segment comprising genomic DNA encoding the B $\beta$  chain; and

a third DNA segment encoding a secretion signal operably linked to a to a heterologous fibrinogen  $\gamma$  chain, the DNA segment comprising genomic DNA encoding the  $\gamma$  chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.